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Schwegman, Lundberg, Woessner & Kluth, P.A.
P.O. Box 2938
Minneapolis, MN 55402

EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/828,708	DITZEL ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/24/01; 11/13/01; 11/19/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *20-32 and 34-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-46 are pending.

2. Applicant's election with traverse of Group I, Claims 1-19 and 33 drawn to immunopolypeptide or antibody that read on the elected species of light chain CDR SEQ ID NO: 36, 43, 50, heavy chain CDR SEQ IDNO: 18, 25 and 32, light chain spacer SEQ ID NO: 84, 91, 98 and 105, Heavy chain spacer SEQ ID NO: 60, 65, 72 and 77, Light chain Variable sequence SEQ ID NO: 4 and Heavy chain Variable sequence SEQ ID NO: 11, filed 11/19/02, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, the requirement of Group I and Groups II-XV is still deemed proper and is therefore made FINAL.

3. Claims 20-32 and 34-46 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-19 and 33 drawn to immunopolypeptide or antibody that read on the elected species of light chain CDR SEQ ID NO: 36, 43, 50, heavy chain CDR SEQ IDNO: 18, 25 and 32, light chain spacer SEQ ID NO: 84, 91, 98 and 105, Heavy chain spacer SEQ ID NO: 60, 65, 72 and 77, Light chain Variable sequence SEQ ID NO: 4 and Heavy chain Variable sequence SEQ ID NO: 11 are being acted upon in this Office Action.

5. The drawings, filed 9/24/01, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

6. Claim 17 is objected to for failing to recite the specific ATCC deposit number and "A" should have been "An".

7. Claims 3, 6, 11, 16, 18 and 19 are objected to as being drawn to non-elected inventions because of the non-elected SEQ ID NOS.

8. The disclosure is objected to because of the following informality: incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on page 33 at lines 13, 15, and 17 and page 34 at lines 3, 8, 11, 14, 20, and 26 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database. Appropriate action is required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-19 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated immunoglobulin antibody Fab fragment that specifically binds to human glucose-6-phosphate isomerase consisting of the variable heavy chain selected from the group consisting of (SEQ ID NOS: 8, 11, 9, 10, 12, 13 and 14) and the variable light chain selected from the group consisting of (SEQ ID NOS: 1, 4, 2, 3, 5, 6 and 7) as shown in Fig 3, (2) An immunopolypeptide that binds to glucose-6-phosphate isomerase with a dissociation constant of no more than about 10^{-7} wherein the immunopolypeptide comprises a variable light chain selected from the group consisting of SEQ ID NO: 1 and 4 and a variable heavy chain selected from the group consisting of SEQ ID NOS: 8 and 11 for detection assays, **does not** reasonably provide enablement for (1) *any* immunopolypeptide that binds to human glucose-6-phosphate isomerase with a dissociation constant of no more than 10^{-7}, (2) *any* isolated immunoglobulin antibody that specifically binds to human glucose-6-phosphate isomerase, (3) *any* immunoglobulin "comprising" *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 or *any* significant "homolog" of *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32, (4) *any* immunoglobulin mentioned above "having" a triplet of any CDR sequences,

(5) *any* immunoglobulin "comprising" *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 or *any* significant "homolog" of *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 having a triplet of *any* CDR sequences wherein each CDR of the triplet is separated from other CDR's by *any* "spacer amino acid sequence", (6) *any* immunoglobulin "comprising" *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 or *any* significant "homolog" of *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 having a triplet of *any* CDR sequences wherein each CDR of the triplet is separated from other CDR's by *any* spacer amino acid sequence which is a framework region "having" an amino acid sequences of SEQ ID NO: 84, 91, 98, 105, 60, 65, 72 and 77 or *any* "significant homolog thereof", (7) *any* immunoglobulin mentioned above wherein the CDR's of the triplet are from either the light chain group or a heavy chain group, (8) *any* immunoglobulin "comprising" *any* significant "homolog thereof" of *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 having a triplet of CDR sequences wherein each CDR of the triplet is separated from other CDR's by *any* "spacer amino acid sequence" wherein the spacer amino acid sequence is a framework region "having" an amino acid sequences significant "homolog thereof" of SEQ ID NO: 84, 91, 98, 105, 60, 65, 72 and 77 wherein the CDR's of the triplet are selected from either a light chain or a heavy chain group wherein the CDR's are matched according to their Fab source, (9) *any* immunoglobulin "comprising" *any* significant "homolog thereof" of any CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 having a triplet of CDR sequences wherein each CDR of the triplet is separated from other CDR's by *any* "spacer amino acid sequence" wherein the spacer amino acid sequence is *any* framework region "having" an amino acid sequences significant "homolog thereof" of SEQ ID NO: 84, 91, 98, 105, 60, 65, 72 and 77 wherein the CDR's of the triplet are selected from either a light chain or a heavy chain group wherein the framework region sequence is matched to the Fab source of the CDR triplet, (10) *any* immunopolypeptide mentioned above wherein the amino acid sequence is *any* V_L or V_H fragment of the Fab source of the matched CDR triple and framework regions, (11) *any* immunopolypeptide having *any* amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11, (12) *any* immunopolypeptide having *any* amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11 which is *any* combination of *any* V_L or V_H, (13) *any* immunopolypeptide having *any* amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11 which is *any* combination of *any* V_L or V_H further includes at least *any* one constant

consensus region, (14) *any* immunopolypeptide having any amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11 which is *any* combination of *any* V_L or V_H in any combination of *any* light chain and *any* heavy chain fragment, (15) *any* immunopolypeptide having a amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11 which is an Fab, Fab', $F(ab')_2$, Fd, scFv or Fv fragment, (16) *any* anti-GPI monoclonal antibody having CDR and framework segments with significant "homology" to *any* amino acid sequences set forth in SEQ ID NOS: 36, 43, 50, 18, 25, 32, 84, 91, 98, 105, 60, 65, 72, and 77, (17) *any* immunopolypeptide encoded in a bacteriophage that is deposited with the ATCC, (18) *any* immunopolypeptide Fab fragment "having" a light variable chain amino acid sequence of SEQ ID NO: 4 and *any* heavy variable amino acid sequence of SEQ ID NO: 11, (19) *any* immunopolypeptide Fab fragment "having" its CDR amino acid sequences of its light chain selected from the group consisting of SEQ ID NO: 36, 43, and 50 and its CDR amino acid sequence of its heavy chain sequence selected from the group consisting of SEQ ID NO: 18, 25 and 32, and (20) *any* pharmaceutical composition comprising *any* immunopolypeptide that binds to human glucose-6-phosphate isomerase with a dissociation constant of no more than about 10^{-7} and a pharmaceutically acceptable carrier for treating any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only seven IgG-derived anti-glucose-6-phosphate isomerase antibodies whose Fab fragment having a variable heavy chain (SEQ ID NO: 8-14) and a variable light chain (SEQ ID NO: 1-7) and a method of making said antibodies. The specification further discloses that only two anti-GPI Fab (A4 and B2) having V_L of SEQ ID NO: 1 and 4 and V_H of

SEQ ID NO: 8 and 11, respectively) exhibited the strongest binding to GPI (page 55) for detecting GPI in synovial fluids of rheumatoid patient by ELISA (page 56).

The specification does not teach how to make *any* immunopolypeptide mentioned above because the phrase "immunopolypeptide" without SEQ ID NO has no structure. There is insufficient guidance as to the structure such as the specific amino acids that makes up the immunopolypeptide, much less treating any disease using any undisclosed immunopolypeptide. Stryer *et al* teach that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages). Without the amino acid sequence of the immunogen, it is unpredictable which undisclosed immunopolypeptide would bind specifically to human glucose-6-phosphate isomerase, let alone binding to human glucose-6-phosphate isomerase with high affinity such as having dissociation constant in the order of no more than 10^{-7}. Further, there is inadequate guidance and working example as to the combination and subcombination of light chain variable region, and heavy chain variable region, much less the substantially homologous of said light chain variable and heavy chain variable region of any immunopolypeptide, in turn, would bind specifically to human glucose-6-phosphate isomerase with a dissociation constant of no more than about 10^{-7}.

Even if the isolated immunoglobulin antibody binds specifically to human glucose-6-phosphate isomerase, there is insufficient guidance as how to use the antibody to effectively treat any disease such as autoimmune rheumatoid arthritis. Kuby *et al* teach that immunizing a peptide such as a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Further, there are no in vivo working examples demonstrating any immunopolypeptide, any antibody that binds to human glucose-6-phosphate isomerase and any pharmaceutical composition comprising any undisclosed immunopolypeptide is effective for treating any disease such as autoimmune disease rheumatoid arthritis. The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering any immunopolypeptide and any antibody that binds to human glucose-6-phosphate isomerase. The specification does not teach how to extrapolate data obtained from in vitro detection assays to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the immunopeptide or antibody that binds to human glucose-6-phosphate exemplified in the specification for treating any disease

such as autoimmune rheumatoid arthritis. A pharmaceutical composition in the absence of in vivo data are unpredictable for the following reasons: (1) the immunopolypeptide or antibody may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the immunopolypeptide or antibody; (2) the immunopolypeptide or antibody may not reach the target area because, i.e. the immunopolypeptide or antibody may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the immunopolypeptide or antibody unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

With regard to "significant homolog thereof", the specification on page 38 defines "significant homology" as any antibody or immunopolypeptide exhibiting at least 80% identity to the reference antibody or immunopolypeptide and sequence identity may be measured using sequence analysis software as long as they exhibit the desired biological activity (See page38-39). However, the specification does not teach which amino acid within the full length immunopolypeptide would tolerate substitution, deletion, or addition and whether the modified immunopolypeptide would retain the desired "biological activity", much less having the same function, in turn, would be useful as a pharmaceutical composition for treating any disease. Since the specification fails to provide guidance regarding which amino acid within the immunopolypeptide can tolerate change and yet maintain the same function, it follows that any homolog thereof is not enable.

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Because applicants have not disclosed the specific condition used to score sequence identity and whether the undisclosed antibody and immunopolypeptide having the same function as the immunopolypeptide or antibody such as B2 and A4 that binds specifically to human glucose-6-phosphate isomerase, it is unpredictable to determine which undisclosed antibody and

immunopolypeptide will retain the same structure, let alone having the same function and would be useful for any purpose.

With regard to "having" in claims 4, 6, and 18-19, the term "having" is open-ended. It expands the immunopolypeptide in claim 4 to include additional amino acids at either or both ends in addition to the triplet of CDR sequences. There is insufficient guidance as to the undisclosed amino acid residues to be added and whether after addition the immunopolypeptide would have same structure and function.

Regarding "a spacer amino acid sequence" as recited in claim 5, the said phrase has no structure without SEQ ID NO. Further, not all amino acid is useful as a spacer given some of the properties such as hydrophobic, hydrophilic, inflexible of some of the amino acid residues. Given the indefinite number of undisclosed amino acid sequence, there is insufficient guidance in the specification as to the structure associated with functional properties of said spacer amino acid sequence linking each of the CDR of the triplet.

With regard to immunopolypeptide encoded in bacteriophage that is deposited with the ATCC, there is insufficient guidance as to which specific immunopolypeptide encoded in the bacteriophage is being deposited with the ATCC. Given the indefinite number of undisclosed immunopolypeptide encoded in bacteriophage that is deposited with the ATCC and the lack of guidance as to the specificity of the undisclosed immunopolypeptide, it is unpredictable which undisclosed immunopolypeptide would bind specifically to human glucose-6-phosphate isomerase with a dissociation constant of no more than about 10^{-7}, in turn, would be useful for any purpose.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 1-19 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* immunopolypeptide that binds to human glucose-6-phosphate isomerase with a dissociation constant of no more than 10^{-7}, (2) *any* isolated immunoglobulin antibody that specifically binds to human glucose-6-phosphate isomerase, (3) *any* immunoglobulin "comprising" *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 or *any* significant "homolog" of *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32, (4) *any* immunoglobulin mentioned above "having" a triplet of any CDR sequences, (5) *any* immunoglobulin "comprising" *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 or *any* significant "homolog" of *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 having a triplet of *any* CDR sequences wherein each CDR of the triplet is separated from other CDR's by *any* "spacer amino acid sequence", (6) *any* immunoglobulin "comprising" *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 or *any* significant "homolog" of *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 having a triplet of *any* CDR sequences wherein each CDR of the triplet is separated from other CDR's by *any* spacer amino acid sequence which is a framework region "having" an amino acid sequences of SEQ ID NO: 84, 91, 98, 105, 60, 65, 72 and 77 or *any* "significant homolog thereof", (7) *any* immunoglobulin mentioned above wherein the CDR's of the triplet are from either the light chain group or a heavy chain group, (8) *any* immunoglobulin "comprising" *any* significant "homolog thereof" of *any* CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 having a triplet of CDR sequences wherein each CDR of the triplet is separated from other CDR's by *any* "spacer amino acid sequence" wherein the spacer amino acid sequence is a framework region "having" an amino acid sequences significant "homolog thereof" of SEQ ID NO: 84, 91, 98, 105, 60, 65, 72 and 77 wherein the CDR's of the triplet are selected from either a light chain or a heavy chain group wherein the CDR's are matched according to their Fab source, (9) *any* immunoglobulin "comprising" *any* significant "homolog thereof" of any CDR sequence such as SEQ ID NO: 36, 43, 50, 18, 25 and 32 having a triplet of CDR sequences wherein each CDR of the triplet is separated from other CDR's by *any* "spacer amino acid sequence" wherein the spacer amino acid sequence is *any* framework region "having" an amino acid sequences significant "homolog

thereof" of SEQ ID NO: 84, 91, 98, 105, 60, 65, 72 and 77 wherein the CDR's of the triplet are selected from either a light chain or a heavy chain group wherein the framework region sequence is matched to the Fab source of the CDR triplet, (10) *any* immunopolypeptide mentioned above wherein the amino acid sequence is *any* V_L or V_H fragment of the Fab source of the matched CDR triple and framework regions, (11) *any* immunopolypeptide having *any* amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11, (12) *any* immunopolypeptide having *any* amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11 which is *any* combination of *any* V_L or V_H, (13) *any* immunopolypeptide having *any* amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11 which is *any* combination of *any* V_L or V_H further includes at least *any* one constant consensus region, (14) *any* immunopolypeptide having any amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11 which is *any* combination of *any* V_L or V_H in any combination of *any* light chain and *any* heavy chain fragment, (15) *any* immunopolypeptide having a amino acid sequence "substantially homologous" to a sequence selected from the group consisting of SEQ ID NO: 4 and 11 which is an Fab, Fab', $F(ab')_2$, Fd, scFv or Fv fragment, (16) *any* anti-GPI monoclonal antibody having CDR and framework segments with significant "homology" to *any* amino acid sequences set forth in SEQ ID NOS: 36, 43, 50, 18, 25, 32, 84, 91, 98, 105, 60, 65, 72, and 77, (17) *any* immunopolypeptide encoded in a bacteriophage that is deposited with the ATCC, (18) *any* immunopolypeptide Fab fragment "having" a light variable chain amino acid sequence of SEQ ID NO: 4 and *any* heavy variable amino acid sequence of SEQ ID NO: 11, (19) *any* immunopolypeptide Fab fragment "having" its CDR amino acid sequences of its light chain selected from the group consisting of SEQ ID NO: 36, 43, and 50 and its CDR amino acid sequence of its heavy chain sequence selected from the group consisting of SEQ ID NO: 18, 25 and 32, and (20) *any* pharmaceutical composition comprising *any* immunopolypeptide that binds to human glucose-6-phosphate isomerase with a dissociation constant of no more than about 10^{-7} and a pharmaceutically acceptable carrier for treating any disease.

The specification discloses only seven IgG-derived anti-glucose-6-phosphate isomerase antibodies whose Fab fragment having a variable heavy chain (SEQ ID NO: 8-14) and a variable light chain (SEQ ID NO: 1-7) and a method of making said antibodies. The specification further discloses that only two anti-GPI Fab (A4 and B2) having V_L of SEQ ID NO: 1 and 4 and V_H of

SEQ ID NO: 8 and 11, respectively) exhibited the strongest binding to GPI (page 55) for detecting GPI in synovial fluids of rheumatoid patient by ELISA (page 56).

With the exception of the specific immunopolypeptide in a specific combination of CDR sequences that binds to human glucose-6-phophate isomerase mentioned above, there is insufficient written description about the structure associated with function of *any* "immunopolypeptide", *any* "homolog thereof", *any* "spacer amino acid sequence", *any* "immunopolypeptide encoded in a bacteriophage that is deposited with the ATCC", *any* immunopolypeptide having *any* amino acid substantially homologous to SEQ ID NO: 1-14 because any "immunopolypeptide", homolog, spacer amino acid sequence, without SEQ ID NO has no structure. Further, the terms "comprising" and "having" are open-ended. It expands the immunopolypeptide to include additional amino acid at either or both ends. There is inadequate written description about the additional undisclosed amino acids to be added to the immunopolypeptide having the specific CDR sequences.

With regard to "significant homolog thereof", the specification on page 38 defines "significant homology" as any antibody or immunopolypeptide exhibiting at least 80% identity to the reference antibody or immunopolypeptide and sequence identity may be measured using sequence analysis software as long as they exhibit the desired biological activity (See page38-39). However, there is insufficient written description about the structure of any "significant homolog thereof", much less about the desired "biological activity", or function, in turn, useful as a pharmaceutical composition for treating any disease.

Further, the specification discloses only seven antibodies to human glucose-6-phosphate isomerase and only two out of the seven antibodies have a dissociation constant of no more than about 10^{-7}. Given the lack of a written description of *any* additional representative species of immunopolypeptide that binds to human glucose-6-phosphate isomerase with a dissociation constant of no more than about 10^{-7}, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 4-10 and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "having" in claims 4, 6, and 18-19 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. If the immunopolypeptide is intended to be open-ended, it is suggested that Applicant amends the claim to recite, "comprising". If the immunopolypeptide is intended to be close-ended, it is suggested that Applicant amends the claim to recite, "consisting of".

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-7 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Yakirevich *et al* (Biology of Reproduction 62: 1016-23, March 2000; PTO 892).

Yakirevich *et al* teach an immunopolypeptide or such as an immunoglobulin antibody mAb A36 that binds to human glucose phosphate isomerase (GPI) (See page 1018, column 2, Results, and page 1019, column 1, in particular). The reference monoclonal antibody also binds to the homologous sequence such as the human sperm antigen (See page 1020, column 2, last paragraph, in particular). Because the dissociation constant is an inherent property of the reference antibody and most antibodies have dissociation constant "about" 10^{-7}, the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The reference immunopolypeptide mAb A36 (10 μg/ml) is in a composition comprising a pharmaceutical acceptable carrier such as Tris-buffer saline (pH 7.4) (See page 1017, column 1, in particular). Claim 3 is included in this rejection because the reference mAb A36 is a significant homolog of

the claimed immunopolypeptide such as antibody to GPI comprising at least one CDR sequence. Claim 4 is included in this rejection because the reference antibody inherently has a triplet of CDR sequences in the variable heavy and light chains, which are part of the antibody structure. Claims 5-6 are included in this rejection because the reference antibody's CDR inherently separated by a spacer amino acid sequence such as the framework region sequence (part of the antibody structure) that hold the CDR together; the reference framework region sequence is a significant homolog of the framework region sequence of the claimed antibody. Claim 7 is included in this rejection because the reference antibody inherently has CDR's of the triplet from either light chain or heavy chain. Thus, the reference teachings anticipate the claimed invention.

16. Claims 3-7 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 520499-A (Dec 1992, PTO 892).

The EP 520499 patent teaches an immunopolypeptide such as a human monoclonal antibody specific for a cancer cell membrane (Mab GAH) having at least one variable light chain region (CDR) consisting of WASTRES, which is 100% identical to the claimed SEQ ID NO: 43 (See page 23, at lines 10 reference SEQ ID NO: 20, in particular). The reference immunopolypeptide Mab GAH has a triplet CDR sequences containing the three variable regions of the heavy and light chains (See page 3 at lines 31-50, claims 1 and 3 or the EP 520499 patent, in particular). The reference triplet CDR wherein each CDR of the triplet is inherently separated from other CDR's by a spacer amino acid sequences such as reference SEQ ID NO: 11 and 12 (See page 19-20, in particular). The reference immunopolypeptide wherein the reference CDR's of the triplet is from a light chain (See claim 3 of the EP 520499-A patent, in particular). The term "comprising" or "having" is open-ended. It expands the claimed sequence to include additional amino acids at either or both end to read on the reference immunopolypeptide. Claim 6 is included in this rejection because the reference CDR inherently has the spacer amino acid sequence such as the framework region that holds the CDR triplet together as part of the reference antibody structure and the reference framework sequence of Mab GAH is also a significant homolog of the claimed framework sequence. Thus, the reference teachings anticipate the claimed invention.

17. Claims 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,419,904 (May 1995, PTO 892).

The '904 patent teaches an immunopolypeptide such as a human monoclonal antibody L612 having an amino acid sequence substantially homologous to the claimed sequence of SEQ ID NO: 4 (See reference SEQ ID NO: 4, in particular). The term "having" is open-ended. It expands the claimed sequence to include additional amino acids at either or both ends. The reference immunopolypeptide is a combination of V_L and V_H (See Figs 1 and 2, column 7, lines 48-53, claims 9 of '904, in particular). The reference immunopolypeptide contains at least one constant consensus region because the reference immunopolypeptide is a human monoclonal antibody with an IgM kappa isotype and the heavy chain and light chain are shown in Figure 1 and 2, respectively (See column 4, line 48-50, Figures 1 and 2, in particular). Thus, the reference teachings anticipate the claimed invention.

18. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,387,414 (Feb 1995, POT 892).

The '414 patent teaches an immunopolypeptide such as recombinant peptide with novel epitope that is unique among known Eimeria antigens encoded in a bacteriophage such as lambda gt11 that is deposited with the ATCC having an accession number 68450 (See Abstract, column 2, at lines 49-53, Claim 1 of '414 patent, in particular). Thus, the reference teachings anticipate the claimed invention.

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 520499-A (Dec 1992, PTO 892) in view of the WO 9311794 publication (June 1992; PTO) or US Pat No. 6,001,358 (Dec 1999; PTO 892) or US Pat No. 5,652,138 (July 1997; PTO 892) or US Pat No. 6,358,710 B1 (March 2002, PTO 892).

The teachings of the EP 520499-A patent have been discussed supra.

The claimed invention as recited in claim 6 differs from the teachings of the reference only that the immunopolypeptide wherein the spacer amino acid sequence is a framework region sequence having an amino acid sequence of selected from the group consisting of SEQ ID NO: 84, 91, 98, 105, 65 and 77 or a significant homolog thereof.

The claimed invention as recited in claim 7 differs from the teachings of the reference only that the immunopolypeptide wherein the CDR's of the triplet is from either the light chain group or a heavy chain group.

The claimed invention as recited in claim 8 differs from the teachings of the reference only that the immunopolypeptide wherein the CDR's are matched according to their Fab source.

The claimed invention as recited in claim 9 differs from the teachings of reference only that the immunopolypeptide wherein the framework region sequence is matched to the Fab source of the CDR triplet.

The claimed invention as recited in claim 10 differs from the teachings of the reference only that the immunopolypeptide wherein the amino acid sequence is a V_L or V_H fragment of the Fab source of the matched CDR triplet and framework.

The WO 9311794 publication teaches a method of making humanized antibody using an immunopolypeptide such as human kappa 4 AAR38598 having the spacer amino acid sequence which is a framework region sequence having an amino acid identical to the claimed SEQ ID NO: 43 to prepare a modified mouse antibody variable domain that reduced immunogenicity in humans (See claim 2, page 898-99, in particular).

The '358 patent teaches a method of making immunopolypeptide such as any humanized antibodies that retain not less than one-tenth of the antigen binding affinity and function of the parent antibodies for treatment of autoimmune disease such as rheumatoid arthritis by CDR grafting on to the reference immunopolypeptide which a spacer amino acid sequence containing human framework region 2 (FR2) and human framework region 3 (FR3) such as the reference SEQ ID NO: 13 where the reference FR2 is 100% identical to the claimed sequence of SEQ ID

NO: 91 (FR2) and the reference FR3 is 100% identical to the claimed SEQ ID NO: 98 (FR3) (See Table column 18, Table 3, reference SEQ ID NO: 13).

The '138 patent teaches a method of making various immunopolypeptide such as a humanized monoclonal antibody that has the framework region amino acid sequence (spacer amino acid sequence FR4) such as SEQ ID NO: 149 that has amino acid residues from 98-149 identical the claimed SEQ ID NO: 105 (See reference SEQ ID NO: 149 from residues 98-149, in particular) and heavy chain spacer amino acid sequence such as SEQ ID NO: 143 that has amino acid residues from 107-117 identical the claimed SEQ ID NO: 77.

The '710 patent teaches an immunopolypeptide having a framework region sequence such as SEQ ID NO: 19 that contains a stretch of amino acid sequence that is 100% identical to the claimed SEQ ID NO: 65 (See reference SEQ ID NO: 19, residues 36-49, in particular). The reference immunopolypeptide is a humanized antibody that is useful for antibody therapy and immunodiagnosis (See abstract, in particular). The '710 patent teaches the framework region of the antibody is to hold the CDRs in appropriate orientation to bind antigen (See column 6, lines 63-67, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute or to graft the framework region sequences such as the FR1, FR2, FR3 and FR4 of the immunopolypeptide such as the human monoclonal antibody specific for a cancer cell membrane (Mab GAH) having at least one variable light chain region (CDR) consisting of WASTRES, which is 100% identical to the claimed SEQ ID NO: 43 (See page 23, at lines 10 reference SEQ ID NO: 20, in particular) as taught by the EP 520499-A patent for the human framework region sequence such as the FR1 as taught by WO 9311794 publication, the FR2 and FR3 as taught by the '358 patent and the FR4 as taught by the '138 patent for an immunopolypeptide having the framework region sequence or spacer amino acid sequence selected from the group consisting of SEQ IDNO: 84, 91, 98 and 105 as taught by The WO 9311794 publication, the '358 patent and the '138 patent. The term "comprising" or "having" is open-ended. It expands the claimed sequence to include additional amino acids at either or both end to read on the reference immunopolypeptide. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because The WO 9311794 publication teaches humanized antibody is useful for reduced immunogenicity of

the antibody in humans (See claim 2, page 898-99, in particular). The '358 patent teaches humanized antibodies that retain not less than one-tenth of the antigen binding affinity and function of the parent antibodies is useful for treatment of autoimmune disease such as rheumatoid arthritis by CDR grafting (See Table column 18, Table 3, reference SEQ ID NO: 13). The '710 patent teaches that humanized antibody that is useful for antibody therapy and immunodiagnosis (See abstract, in particular). Claims 8-10 are included in this rejection because the EP 520499 patent teaches an immunopolypeptide such as human monoclonal antibody and the CDR of the reference human monoclonal antibody obviously matched with source of the human Fab fragment and substituting the framework region sequence from human monoclonal antibody as taught by the EP 520499 patent for the human framework region sequence as taught by the WO 9311794 publication, the '358 patent, the '138 patent, and the '710 patent obviously matched to the human Fab source of the CDR triplet. Likewise, the amino acid sequence of the variable light chain or the variable heavy chain of the human monoclonal antibody which are part of the CDR triplet of the Fab source as taught by the EP 520499 patent obviously matched with the human framework regions as taught by the EP 520499 patent, the WO 9311794 publication, the '358 patent, the '138 patent, and the '710 patent.

22. Claims 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,419,904 (May 1995, PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629).

The teachings of the '904 patent have been discussed supra.

The claimed invention as recited in claim 15 differs from the teachings of the reference only that the immunopolypeptide is a Fab, or $F(ab')_2$.

Harlow *et al* teach a method of producing antibody fragment wherein the fragment is Fab fragment (See page 626-629, in particular). Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce antibody fragment such as Fab or $F(ab')_2$ antibody as taught by Harlow *et al* with the antibody as taught by the '904 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach antibody fragments can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular) and the labeled antibody can be used for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

23. Claims 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,419,904 (May 1995, PTO 892) in view of US Pat No. 5,260,203 (Nov 1993, PTO 892) or Barbas *et al* (Proc. Natl. Acad. Sci USA 88: 7987-82, 1991; PTO 892).

The teachings of the '904 patent have been discussed supra.

The claimed invention as recited in claim 15 differs from the teachings of the reference only that the immunopolypeptide is an Fd, scFv or Fv fragment.

The '203 patent teaches a method of producing any single chain antibody (also known as svFv) such as Fv fragment comprising the antigen binding portion of the light chain variable region linked to the antigen binding portion of the variable region of any antibody (See column 29, lines 25 bridging column 30, lines 1-20, claims of '203, in particular). The advantages of a single chain antibody are: small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Barbas *et al* teach a method of producing any high-affinity antigen specific Fabs such as Fd comprising heavy chain variable region and heavy chain constant region 1 domains linked via a flexible five-amino acid tether from combinatorial antibodies phagemid vector pComb3 (See entire document, page 7980, column 1, second full paragraph, in particular). The advantage of using monovalent display (Fd) over multivalent display is that it allows for sorting of clones based on affinity as well as specificity, much like the immune system (See page 7980, column 2, first full paragraph, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to make any single chain antibody as taught by the '203 patent or the Fd as taught by Barbas *et al* that binds specifically to the immunopolypeptide as taught by the '904

patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '203 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular). Barbas *et al* teach the advantage of using monovalent display (Fd) over multivalent display is that it allows for sorting of clones based on affinity as well as specificity, much like the immune system (See page 7980, column 2, first full paragraph, in particular).

24. Claims 16, 18 and 19 are free of prior art.

25. No claim is allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

27. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
January 27, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600